Genetic Screening to Prevent Abacavir Hypersensitivity Reaction: Are We There Yet?

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(See the article by Rauch et al. on pages 99–102)

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Pharmacogenetics is hardly a new field, with early discoveries of genetic differences in drug-metabolizing enzymes dating back to the early 1960s. However, despite the increasing knowledge base regarding variation in drug response and toxicity related to pharmacogenetic factors and the simplification and increased availability of molecular technologies, there have been major barriers to the introduction of genetic testing into routine clinical practice [1]. Factors favoring uptake of a genetic test into clinical practice are shown in table 1. The lack of incorporation of testing into practice has related primarily to (1) the availability of laboratory markers that correctly phenotype drug response or toxicity (e.g., drug levels for anticonvulsants or international normalized ratio for warfarin), (2) the lack of standardized clinical or laboratory guidelines or algorithms for the interpretation of genetic test results, and (3) the paucity of evidence-based medicine showing that the prospective use of pharmacogenetic screening positively impacts patient outcome.

Abacavir hypersensitivity reaction is a potentially life-threatening disease that occurs in ~5% of patients initiating therapy with this drug. It sets itself apart from the majority of other drug toxicities encountered in clinical practice—which tend to be multifactorial in etiology, dose related, and pharmacologically predictable—in that its occurrence appears to be largely unrelated to dose, and its clinical presentation is more severe in cases of reexposure. Furthermore, clinical diagnosis of this disease (which most commonly presents 9–11 days after initiation of therapy) has been confounded by an overlap of symptoms and signs with those of other drug hypersensitivities, viral infections, and immune restoration diseases. Although the occurrence of abacavir hypersensitivity reaction has been more common in Caucasian subjects (occurring in 8% of such subjects who initiate abacavir therapy), other clinical factors have not been useful in the prediction of this disease, and the risk of morbidity and even mortality on rechallenge precludes future use of abacavir in an individual who has been labeled with abacavir hypersensitivity syndrome.

A major breakthrough occurred in 2002 with the publication by 2 independent groups of a strong association between a specific HLA *(HLA-B*5701)* and abacavir hypersensitivity reaction [2, 3]. In this issue of *Clinical Infectious Diseases,* one of these groups—from Perth, Western Australia—describes their experience with the implementation of prospective screening for *HLA-B*5701* in a single-center cohort since January 2002, compared with their experience in the prescreening era from January 1998 through December 2001 [4]. Convincingly, this study has shown that, of 148 patients found to be *HLA-B*5701* negative and exposed to abacavir since January 2002, only 6 patients (4%) had abacavir discontinued within 6 weeks; all 6 of these patients had presentations clinically inconsistent with abacavir hypersensitivity reaction (nonspecific symptoms, single-symptom disease, or symptoms that did not respond to abacavir dechallenge). These patients were also found to have negative results of patch testing, which has emerged as a promising diagnostic technique for confirmation of abacavir hypersensitivity reaction [5]. Of note, among 151 patients exposed to abacavir, each of the 3 patients who developed convincing clinical evidence of abacavir hypersensitivity reaction had been *HLA-B*5701* positive on screening, with 2 of these 3 patients being inadvertently exposed to abacavir because of a lack of review of HLA results before abacavir prescription and 1 of these 3 patients being exposed

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Table 1. Factors favoring implementation of a pharmacogenetic test into clinical practice.

Application of test improves clinical outcome
Ready availability and/or rapid low-cost test
High predictive value of test
Identification of clinical parameters that determine usefulness
Ease of incorporation into routine management

on the basis of his own consent. All 3 of these patients had strongly positive abacavir patch test results. Overall, despite the prescription of abacavir for 3 patients known to be *HLA-B*5701* positive, this group was able to show a statistically significant decrease in the incidence of "true" abacavir hypersensitivity reaction, from 8% in the era before genetic screening for *HLA-B*5701* to 2% after the implementation of genetic screening.

There are several important conclusions and implications of this study that should be highlighted. First, this is one of the first studies in which prospective implementation of a pharmacogenetic screening test that requires a yes or no interpretation has been shown to convincingly reduce the occurrence of a defined toxicity. Perhaps of even more interest, this study has shown not only that implementation of genetic screening was associated with a significant reduction in the incidence of true abacavir hypersensitivity but also that the incidence of overall early abacavir discontinuations decreased from 16.5% in the prescreening era to 6% after screening was implemented [4]. One might interpret this as implying that we have become better at the clinical diagnosis of abacavir hypersensitivity reaction over time; however, other groups not using screening have, in fact, seen an increase in early discontinuation of abacavir therapy since 2001 [6]. An alternate explanation is that genetic screening provides additional information that allows clinical pharmacovigilence to be applied more intelligently to an individual patient population.

Where does this leave us in terms of the application of genetic screening for *HLA-B*5701* to our own clinic populations initiating abacavir therapy? First, there are several practical issues with regard to broad-based application of screening to HIV clinic populations. Clearly, the utility, cost-effectiveness, and generalizability of genetic screening to a given clinic population will depend on knowledge of the prevalence of *HLA-B*5701* in that population, which has been shown to be closely linked to the incidence of abacavir hypersensitivity reaction in a given population. In clinics serving a predominantly Caucasian population, the overall incidence of abacavir hypersensitivity is 5%–8%, which means that, from a feasibility and cost-effectiveness standpoint, only ~14 patients would need to be screened to prevent 1 case of abacavir hypersensitivity reaction. However, this ratio would be much less cost-effective in certain Asian and African black populations, for whom the prevalence of *HLA-B*5701* is <1% (figure 1). The wide range of frequencies of abacavir hypersensitivity reaction described in clinical trials (0%–14%) is at least in part attributable to ethnic or racial differences in enrollees in these studies. Regardless, the clinical implications of *HLA-B*5701* positivity appear to be the same, and we assume that an *HLA-B*5701*–positive African black subject is just as likely to experience abacavir hypersensitivity reac-

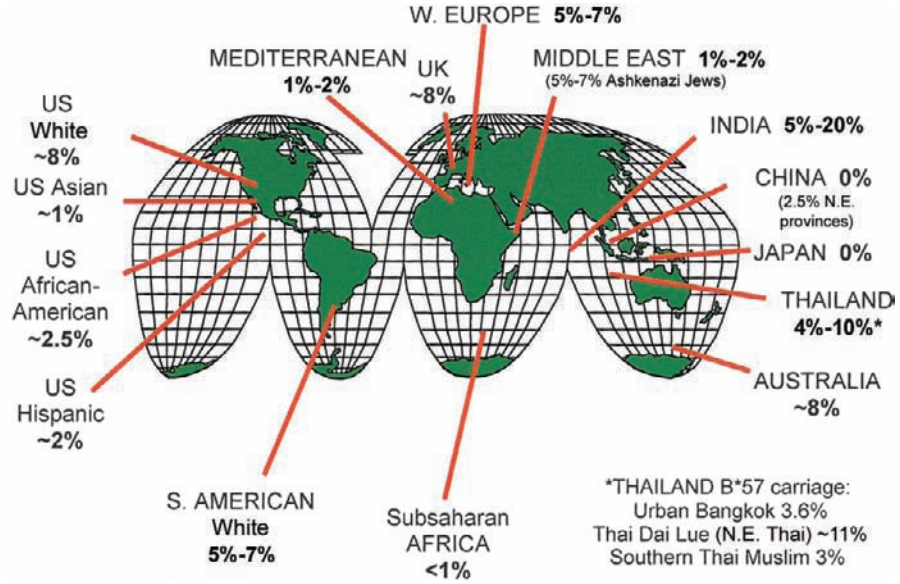

Figure 1. The prevalence of *HLA-B*5701* in different parts of the world. These carriage frequencies mirror the incidence of abacavir hypersensitivity in exposed individuals. Adapted from [7].

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tion as an *HLA-B*5701*–positive Caucasian subject. In addition, data from patch testing studies, which to date have shown 100% correlation between positive patch test results and *HLA-B*5701* positivity (and which have identified no other genetic markers independently associated with abacavir hypersensitivity reaction), have been reassuring [8, 9].

At the end of the day, we have to be clear about both what we can and what we cannot currently accomplish with *HLA-B*5701* screening for abacavir hypersensitivity reaction. The data from Western Australia [4] reassures us that genetic screening can prevent true abacavir hypersensitivity and, intriguingly, may also lower the rate of false-positive diagnosis of abacavir hypersensitivity syndrome. Screening, therefore, shows promise to be cost-effective, both by lowering the morbidity associated with true hypersensitivity reactions and by reducing inappropriate early discontinuation of therapy. Importantly, a point that is often overlooked is that screening should actually significantly increase the safety of abacavir use by promoting proactive avoidance of abacavir use in the *HLA-B*5701*–positive population, who would be at risk for death as the result of inadvertent rechallenge with abacavir.

Genetic screening for abacavir hypersensitivity reaction also warrants a few words of caution. Screening should promote a more intelligent pharmacovigilence, but it should in no way be used as a substitute for clinical judgment or pharmacovigilence. A large, randomized, controlled trial is planned that will enroll subjects from sites in Europe and Australia; this trial will provide more-definitive information on the utility and generalizability of *HLA-B*5701* screening in diverse populations. At this time, *HLA-B*5701* screening is best positioned as a screening test for abacavir-naive populations and should not be used as a rationale for rechallenge in abacavir-exposed individuals. Because high-resolution HLA typing is costly, is performed in specialized immunology and transplant laboratories, and has long turnaround times, more-rapid and cheaper validated molecular tests, such as the recently published *HLA-B57* sequence-specific amplification and flow cytometric techniques, will be welcomed [10, 11]. Rauch et al. [4], in their description of 2 *HLA-B*5701*–positive patients who were inadvertently exposed to abacavir despite positive screening results, emphasize an important point: genetic screening will simply not work unless the test results are acted upon! Ensuring the reliable and timely transmission of information from laboratory to clinician will be vital to the safety and success of such genetic screening programs.

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